Modeling preeclampsia using human induced pluripotent stem cells.

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Public Summary:
Using induced pluripotent stem cells (iPSC) derived from placental cells from patients that developed preeclampsia (PE) during pregnancy, we were able to model this disease in the dish. Evaluation of placental cell types derived from these iPSC showed that the PE-associated iPSC could make normal placental progenitor cells but were defective in making syncytiotrophoblast, placental cells that are specialized in gas and nutrient exchange. We also showed that PE-associated iPSC had an abnormal response to changes in oxygen tension in their microenvironment. These abnormalities recapitulate patterns of injury seen in placentas of patients with PE, and show that iPSC can in fact model this complex pregnancy-associated disease in the dish.

Scientific Abstract:
Preeclampsia (PE) is a pregnancy-specific hypertensive disorder, affecting up to 10% of pregnancies worldwide. The primary etiology is considered to be abnormal development and function of placental cells called trophoblasts. We previously developed a two-step protocol for differentiation of human pluripotent stem cells, first into cytotrophoblast (CTB) progenitor-like cells, and then into both syncytiotrophoblast (STB)- and extravillous trophoblast (EVT)-like cells, and showed that it can model both normal and abnormal trophoblast differentiation. We have now applied this protocol to induced pluripotent stem cells (iPSC) derived from placentas of pregnancies with or without PE. While there were no differences in CTB induction or EVT formation, PE-iPSC-derived trophoblast showed a defect in syncytialization, as well as a blunted response to hypoxia. RNAseq analysis showed defects in STB formation and response to hypoxia; however, DNA methylation changes were minimal, corresponding only to changes in response to hypoxia. Overall, PE-iPSC recapitulated multiple defects associated with placental dysfunction, including a lack of response to decreased oxygen tension. This emphasizes the importance of the maternal microenvironment in normal placentation, and highlights potential pathways that can be targeted for diagnosis or therapy, while absence of marked DNA methylation changes suggests that other regulatory mechanisms mediate these alterations.